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Health and Environmental Effects Profile for Dimethyl Sulfate

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16. ABSTRACT

The Health and Environmental Effects Profile for dimethyl sulfate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for dimethyl sulfate.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DIMETHYL SULFATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
DNA	Deoxyribonucleic acid
i.v.	Intravenous
K_{oc}	Soil sorption coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
RNA	Ribonucleic acid
RQ	Reportable quantity
s.c.	Subcutaneous
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Dimethyl sulfate, the common chemical name of this compound, is also known as methyl sulfate, sulfuric acid-dimethyl ester and DMS. The structure, molecular weight and empirical formula for dimethyl sulfate are as follows:

Molecular weight: 126.13

Empirical formula: $C_2H_6O_4S$

The CAS Registry number for dimethyl sulfate is 77-78-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dimethyl sulfate occurs as a colorless, oily liquid with a faint onion-like odor (Sandmeyer, 1981). Selected physical properties are listed below:

Melting point:	-31.8°C (McCormack and Lawes, 1983)
Boiling point:	188.8°C (McCormack and Lawes, 1983)
Specific gravity, 20/20°C:	1.328 (McCormack and Lawes, 1983)
Refractive index, 20°C:	1.3874 (McCormack and Lawes, 1983)
Autoignition temperature:	188°C (McCormack and Lawes, 1983)
Flash point (open-cup):	116°C (McCormack and Lawes, 1983)
Water solubility:	28,000 ppm at 18°C (McCormack and Lawes, 1983) 28,000 ppm at 25°C (U.S. EPA-NIH, 1984)
Vapor pressure, mm Hg	
at room temperature	0.1 (IARC, 1974)
at 20°C	<1 (Verschueren, 1983)
at 76°C	15 (U.S. EPA-NIH, 1984)
at 20°C	0.5 (ACGIH, 1980)
at 20°C	0.68 (Weber et al., 1981)

Dimethyl sulfate is moderately polar and is miscible with most common organic solvents (McCormack and Lawes, 1983).

Chemically, dimethyl sulfate is considered quite reactive; it will react with almost all types of compounds with unshared electron pairs (McCormack and Lawes, 1983). The methylating activity of dimethyl sulfate has commercial applications. Dimethyl sulfate hydrolyzes readily in neutral water, and decomposes when heated to ~200°C (McCormack and Lawes, 1983).

1.3. PRODUCTION DATA

The only current industrial manufacturer of dimethyl sulfate in the United States is E.I. duPont de Nemours and Company in Belle, WV and Grasselli, NJ (SRI, 1984). Production data available from the U.S. EPA's TSCA Production File for 1977 are listed in Table 1-1. In 1977, DuPont manufactured between 20 and 100 million pounds of dimethyl sulfate. In 1980, worldwide production of dimethyl sulfate was estimated to be ~132 million pounds (McCormack and Lawes, 1983). Data regarding the current production of dimethyl sulfate in the United States were not located in the available literature.

Dimethyl sulfate is commercially produced in a continuous operation by reacting dimethyl ether with liquid sulfur trioxide (McCormack and Lawes, 1983).

1.4. USE DATA

Dimethyl sulfate is used as a methylating agent for fabric softeners, agrichemicals, dyes, synthetic drugs and various intermediates (Kuney, (1984). The major methylating uses are in the syntheses of quaternary ammonium salts and long-chain alcohol sulfates (McCormack and Lawes, 1983).

TABLE 1-1

Dimethyl Sulfate Production Data*

Producer	1977 Production (million lbs)
DuPont	
Belle, WV (manufacturer)	10-50
Linden, NJ (manufacturer)	10-50
Haven Chemical	
Philadelphia, PA (small manufacturer)	confidential
Ashland Chemical	
Dublin, OH (importer)	0
Armstrong Chemical	
Jamesville, WI (importer)	confidential
Toms River Chemical	
Toms River, NJ (importer)	confidential
Sakai Trading NY	
NY, NY (importer)	0

*Source: U.S. EPA, 1977

Dimethyl sulfate may, in combination with boron compounds, be used to stabilize liquid sulfur trioxide. The toxicity of dimethyl sulfate precludes its use as a general-purpose solvent (McCormack and Lawes, 1983). In the past, dimethyl sulfate was used as a war gas because it carries no sensing or warning properties (Sandmeyer, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

As with other compounds, the fate of dimethyl sulfate in water will depend on its ability to undergo chemical, photochemical and biological reactions and to partition from the water column into air or sediment. Aqueous hydrolysis studies suggest that not only is hydrolysis likely to be the predominant fate process, it is also likely to be responsible for a rapid decomposition of dimethyl sulfate in the water environment. Robertson and Sugamori (1966) examined the kinetics of dimethyl sulfate hydrolysis in distilled water (to which a backing electrolyte, potassium methylsulfate, was added to give a 0.002 M solution) over a range of temperatures. The following rate equation was determined: $\log k = (-7609.092/T)-22.1323 \log T+76.5044$, where k is the rate constant in sec^{-1} and T is the temperature in °K. The rate constants and corresponding half-lives at various temperatures are shown in Table 2-1.

Lee et al. (1980) examined the hydrolysis of dimethyl sulfate in water, dilute acid and dilute base. Within a 24-hour period the dimethyl sulfate was hydrolyzed completely to monomethyl sulfate; however, the monomethyl sulfate persisted over a period of several weeks. These results are consistent with those of Robertson and Sugamori (1966). The following hydrolysis reaction of water with dimethyl sulfate would be expected to occur in the environment (Lee et al. 1980):

$$(CH_3O)_2SO_2 + H_2O \rightarrow CH_3OH + CH_3OSO_3H$$

Pertinent data regarding photolysis or microbial degradation of dimethyl sulfate were not located in the available literature cited in the Appendix.

TABLE 2-1

Hydrolysis Rate Constants and Half-Lives of Dimethyl Sulfate*

Temperature (°C)	k (sec^{-1})	Half-Life (hours)
5	0.0000112	17.2
15	0.0000457	4.2
20	0.000088	2.2
25	0.000166	1.2
35	0.0007688	0.25

*Source: Robertson and Sugamori, 1966

An abstract of a Russian study (Kataeva and Khoroshavin, 1981) reported that strains of SO_4^{-2} reducing bacteria, activated in part by dimethyl sulfate, can be used in the biological treatment of mine wastewaters containing sulfates.

The transport of dimethyl sulfate in the aquatic environment will depend on its ability to volatilize, to adsorb to suspended particulate matter and sediment, or to bioaccumulate in aquatic organisms. Specific experimental data for these transport mechanisms were not found. The water solubility (28,000 ppm) and vapor pressure (~0.5 mm Hg) can be used to calculate a Henry's Law Constant of ~3×10^{-6} atm-m^3/mol. This value of Henry's Law Constant is associated with a slow rate of volatilization (Lyman et al., 1982). The equilibrium water-to-air ratio of dimethyl sulfate can be calculated (Swann et al., 1983) to be >8000. Therefore, volatilization is not significant in relation to hydrolysis. Also, the relatively low K_{oc} value (0.5) estimated for dimethyl sulfate (Section 2.3.) suggests that adsorption to particulate matter and sediment is not significant.

A BCF can be estimated from the following equation presented by Kenaga (1980):

$$\text{Log BCF} = 2.791 - 0.564 \text{ Log WS} \pm 1.99 \text{ orders of magnitude (95\% confidence limit)} \qquad (2\text{-}1)$$

where WS is the water solubility in ppm. Using a WS of 28,000 ppm, a BCF value of 2 is calculated; therefore, dimethyl sulfate is unlikely to bioaccumulate significantly in aquatic organisms.

2.2. AIR

The atmospheric chemical removal processes include reaction with hydroxyl or other radicals, reaction with ozone or photolytic reactions.

Data specific to these reaction processes and dimethyl sulfate were not found. Lee et al. (1980) suggested that dimethyl sulfate emitted to the atmosphere in fly ash and particulate matter from the burning of coal will have an atmospheric residence time of hours to days, and the dimethyl sulfate degradation resulting from hydrolysis will form the monomethyl sulfate.

The physical removal processes include dissolution, adsorption on aerosol particles and dry deposition. The latter two processes are unlikely to have any significance. Dissolution may have some significance because of the relatively high water solubility of dimethyl sulfate. Cupitt (1980) developed the following equation to predict the atmospheric half-life that is due to dissolution, assuming a homogeneous atmosphere of 8 km height and an annual rainfall of 0.75 m: $t_{1/2} = 7.17 \times 10^{-3} P/X$ years, where P is the saturation vapor pressure and X is the saturation mole fraction. For dimethyl sulfate, the half-life can be calculated to be ~0.9 years. Under proper localized conditions, washout by rain or snow may be more significant than the calculated half-life indicates; however, washout by rain or snow does not appear to be nearly as important as the "hours to days" residence time suggested by Lee et al. (1980), which is due possibly to the hydrolysis of this compound by moisture present in ambient air.

2.3. SOIL

The fate and transport of dimethyl sulfate has received virtually no attention in the available literature; however, the significance of aqueous hydrolysis (see Section 2.1.) and the high methylating reactivity of dimethyl sulfate suggests that, because of these chemical removal mechanisms, dimethyl sulfate may decompose rapidly in the soil environment. Pertinent data regarding photolysis or microbial degradation in the soil were not located in the available literature cited in the Appendix.

The following equations have been developed to predict the K_{oc} values of an organic compound from its WS:

$$\text{Log } K_{oc} = 3.64\text{-}0.55 \text{ Log WS (in ppm)} \quad \text{(Kenaga, 1980)} \qquad (2\text{-}2)$$

$$\text{Log } K_{oc} = 0.44\text{-}0.54 \text{ Log WS (in mole fraction)} \quad \text{(Karickhoff et al., 1979)} \qquad (2\text{-}3)$$

The calculated K_{oc} values for dimethyl sulfate from equations 2-2 and 2-3 are 16 and 54, respectively. These values indicate that dimethyl sulfate is not likely to be bound tightly to organic matter in soil and may therefore leach easily from many soils. No experimental adsorption data were found.

The volatility of dimethyl sulfate from the soil has not been investigated. The volatility of a chemical in soil is directly proportional to the vapor pressure and inversely proportional to the WS and soil sorption (Swann et al., 1983). Chemical degradation, in particular, and leaching may be a great deal more significant environmentally than is the soil volatility of dimethyl sulfate under normal conditions.

3. EXPOSURE

3.1. WATER

Pertinent data regarding environmental exposure to dimethyl sulfate in water were not located in the available literature cited in the Appendix. The U.S. EPA STORET Data Base reports no observations for dimethyl sulfate.

3.2. FOOD

Pertinent data regarding exposure to dimethyl sulfate in food were not located in the available literature cited in the Appendix.

3.3. INHALATION

Lee et al. (1980) detected dimethyl sulfate and monomethyl sulfate (hydrolysis product of dimethyl sulfate) in fly ash and in airborne particulate matter generated by coal combustion processes. Analysis of fly ash and airborne particulate matter from a modern, coal-fired heating plant burning low-sulfur (0.5%) high-ash (14%) coal produced the following results: fly ash, 0.74-0.84 μmol/g dimethyl sulfate, 0.44-1.9 μmol/g monomethyl sulfate; particulate matter, 0.07-0.34 μmol/g dimethyl sulfate, 0.22-0.88 μmol/g monomethyl sulfate. These quantitative measurements were considered lower limits because of the hydrolysis of the products during the analysis methods used. In addition to these results, Lee et al. (1980) also detected comparable concentrations of the methylated sulfates in another large, coal-burning power plant. They suggested that their results indicate the concentration of methylated sulfates to be as high as 1000 ppm in primary respirable particulate matter (<1 μm) from coal-fired plants. Dimethyl sulfate and monomethyl sulfate were found to constitute only ~0.5% of the total sulfur in the samples analyzed. Lee et al. (1980) suggested that dimethyl sulfate could be formed by the following reaction:

$$5\ CO(g) + SO_2(g) + 3H_2O(g) \rightarrow (CH_3O)_2SO_2(\ell) + 3\ CO_2(g)$$

If this is correct, then dimethyl sulfate could be formed during the combustion of other sulfur-bearing fuels.

3.4. DERMAL

Pertinent data regarding dermal exposure to dimethyl sulfate were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of dimethyl sulfate were not located in the available literature cited in the Appendix, although the results of experimental and epidemiological studies (Chapter 5) imply that dimethyl sulfate is absorbed readily after inhalation.

4.2. DISTRIBUTION

Four hours after injecting six male Wistar rats intravenously with 80 mg/kg of ^{14}C-dimethyl sulfate, Swann and Magee (1968) found that the amount of radioactive 7-methylguanine as a percentage of the total DNA guanine was reported to be 0.008% in the liver, 0.014% in the lung, 0.046% in the brain and 0.052% in the lungs.

4.3. METABOLISM

Six male rats, each weighing ~170 g, were anesthetized with an intraperitoneal injection of sodium pentobarbital followed by an intravenous injection of 75 mg/kg of dimethyl sulfate (Swann, 1968). Blood was collected from the abdominal aorta of six rats 1 minute after treatment, from two rats 2 minutes after treatment, from two rats 3 minutes after treatment and from five rats 5 minutes after treatment. No dimethyl sulfate was identified in the blood taken from rats 3 or 5 minutes after treatment, indicating a very rapid disappearance of dimethyl sulfate from the bloodstream of rats. Swann (1968) concluded that dimethyl sulfate breaks down quickly in the first organs in which it is distributed (i.e., brain and lungs) (see Section 4.2.). The experimental design, however, does not provide a means of identifying the location (i.e., intravenous or within specific organs) of spontaneous degradation of dimethyl sulfate. Loefroth et al. (1974) reported the presence of ^{3}H-7-methylguanine, ^{3}H-3-methyladenine and

^{3}H-1-methyladenine in the urine after the inhalation of ^{3}H-methyl sulfate by mice. Methylated purines in the urine arising from the methylation of nucleic acids by dimethyl sulfate accounted for 0.15-0.3% of the dose. Additional details are provided in Section 4.4.

Dahl and Hadley (1983) reported that formaldehyde was formed following in vitro incubation of dimethyl sulfate with rat liver microsomes, but not with rat nasal mucosa microsomes.

4.4. EXCRETION

Groups of four mice were exposed by inhalation to 0.00032 or 0.0163 mg/ℓ of ^{3}H-dimethyl sulfate in air for 60 and 135 minutes, respectively. These concentrations corresponded to 2.2 and 250 μCi, respectively (Loefroth et al., 1974). The authors assumed that mice have a minute volume of 24 mℓ. The urine was collected for 48 hours after treatment and ^{3}H-7-methylguanine, as well as small amounts of ^{3}H-3-methyladenine and ^{3}H-1-methyladenine, were identified by paper chromatography. Within 24 hours after exposure to the high concentration, 187 nCi of radioactivity from ^{3}H-7-methylguanine was recovered from the urine; in addition, 98 nCi of radioactivity from ^{3}H-7-methylguanine was identified in the urine within the second 24-hour period following treatment. Methylated purines in the urine arising from the methylation of nucleic acids by dimethyl sulfate accounted for 0.15-0.3% of the dose. The amount of radioactive methylated purines as a fraction of total urinary activity within the first 48 hours after exposure changed by a factor of ~2 (31×10^{-4} to 15×10^{-4}), although the estimated dose difference between the high and low dose groups was >100. Loefroth et al. (1974) concluded that almost any dose of dimethyl sulfate, however small, would result in the methylation of nucleic acids.

5. EFFECTS

5.1. CARCINOGENICITY

In a German study reported in abstract form, Schoegel and Bannasch (1970) exposed groups of 10 Golden hamsters, Wistar rats and NMRI mice of each sex to dimethyl sulfate vapor at concentrations of 0.5 or 2.0 ppm, 6 hours/day, 2 days/week for 15 months. The animals were observed for an additional 15-month period. Tumors were observed in the lungs, thorax and nasal passages as indicated in Table 5-1; however, the tumor occurrence was not associated with species or dose, and control data were incompletely reported.

As reviewed by IARC (1974), an apparently increased incidence of nervous tissue tumors occurred in BD rats exposed to 3 ppm (N=20) or 10 ppm (N=27) of dimethyl sulfate vapor for 1 hour/day, 5 days/week for 130 days (Druckrey et al., 1970). IARC (1974) indicated that 15 high dose rats survived for 643 days and 3 low dose rats died with tumors. After 643 days, the high dose group had one rat with a cerebellar tumor. The low dose group had two rats with tumors in the nervous system. Although there was no mention of a matched control group, in a later report, Druckrey (1973) stated that the spontaneous rate of neurological tumors in BD rats was <1 per 1000. In addition to the nervous system tumors observed by Druckrey et al. (1970), one rat had squamous carcinoma of the nasal epithelium in the low dose group, three rats had squamous carcinoma of the nasal epithelium in the high dose group and one high dose rat had a lymphosarcoma of the thorax with multiple metastases to the lung. The study by Druckrey et al. (1970) is summarized in Table 5-2.

TABLE 5-1

Chronic Animal Tumor Incidence[a]

Agent: Dimethyl Sulfate

Exposure Route	Species/Strain	Dose/Exposure	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	10 hamsters/golden 10 rats/Wistar 10 mice/NMRI	0.5 or 2.0 ppm, 6 hours/day x 2 days/week	15 months	30 months	vapor	lung	carcinoma, degenerate adenom benign adenoma	3 tumors 2 tumors 5 tumors[b]
						thorax nasal passages	sarcoma, carcinoma	1 tumor 6 tumors

QUALITY OF EVIDENCE

Strengths of Study: The animals were exposed and observed for a significant portion of their lifespan.

Weakness of Study: Control data were incompletely reported, and tumor occurrence was not associated with species or dose.

Overall Adequacy: Limited

[a]Source: Schlogel and Bannasch, 1970

[b]It was noted that benign lung adenomas were equally frequent in experimental and control animals (7 tumors, but size of control group was not stated).

TABLE 5-2

Tumor Incidence in 80 Rats[a]

Agent: Dimethyl Sulfate

Exposure Route	Number	Dose/Exposure	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	27	10 ppm	1 hour, 5 days/week for 130 days	643 days	vapor	cerebellum	NS	1/15
						nasal cavity	squamous carcinoma	3/15
						thorax	lymphosarcoma[c]	1/15
Inhalation	20	3 ppm	1 hour, 5 days/week[b] for 130 days	643 days[b]	vapor	nervous system	neurocytoma	1/NR
							aethesioneuro-epithellioma of olfactory nerve	1/NR
						nasal cavity	squamous carcinoma	1/NR
s.c.	NR	50 mg/kg	once	NR[d]	aqueous solution	injection site	sarcomas[e]	7/15
i.v.	12	2 mg/kg/week	800 days	800 days	NR	NA	NA	0/12
	12	4 mg/kg/week	800 days	800 days	NR	NA	NA	0/12

QUALITY OF EVIDENCE

Strengths of Study: The length of the observation period is sufficient for tumor development.

Weakness of Study: No controls; too few animals; animals not separated by sex; some irrelevant routes of exposure; only one species

Overall Adequacy: Limited

[a]Source: Druckrey et al., 1970

[b]Although the durations were not stated explicitly, they were implied in the review by IARC (1974).

[c]Multiple metastases to the lung

[d]Tumors appeared between 314 and 740 days.

[e]Multiple metastases to the lung in three cases

NR = Not reported; NS = not specified; NA = not applicable

In another study reviewed by IARC (1974), subcutaneous injection of 8 mg/kg/week for 394 days and 16 mg/kg/week for 343 days resulted in the development of sarcomas at or near the site of injection in 7/11 and 4/6 surviving rats, respectively (Druckrey et al., 1966). Metastases to the lungs occurred in several cases (4/17). One of the rats receiving 8 mg/kg/week developed hepatic carcinoma. These data are summarized in Table 5-3. In a subsequent study (Druckrey et al., 1970), a single subcutaneous injection of 50 mg/kg resulted in the development of local sarcomas of connective tissue in 7/15 rats within 740 days of treatment (see Table 5-2).

No tumors developed in rats (N=12) injected intravenously once a week with 2 or 4 mg/kg of dimethyl sulfate for 800 days (Druckrey et al., 1970) (see Table 5-2). Druckrey et al. (1970) treated eight pregnant BD rats on day 15 of gestation with a single intravenous injection of dimethyl sulfate. As stated in the review of this study by IARC (1974), three nervous system tumors developed in 7/59 offspring that were observed for >1 year. No control data were reported. According to a review of this study by Druckrey (1973), however, 4/59 offspring had malignant tumors of the nervous system, while 2/59 offspring had malignant hepatic tumors. No control data were reported; Druckrey (1973) stated that the spontaneous rate of neurological tumors in the BD rats was <1 per 1000. The data presented by Druckrey (1973) are summarized in Table 5-4.

IARC (1979) reviewed an unpublished epidemiological study by Pell (n.d.). Among an unspecified number of workers occupationally exposed to dimethyl sulfate, 6 died of cancer versus the expected mortality of 2.4. Respiratory tract cancer was responsible for 3 of the deaths versus the expected mortality of 1.02. Neither the increased incidence of respiratory tract cancer nor the increased rate of cancer at all sites were statistically significant. Further details were not provided.

TABLE 5-3

Animal Tumor Incidence by Subcutaneous Injection[a]

Agent: Dimethyl Sulfate

Species/ Strain	Dose	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
BD rats	8 mg/kg/week	394 days	NR	oil	injection site liver	sarcoma carcinoma	7/11[b,c] 1/6
BD rats (n=8)	16 mg/kg/week	343 days (49 weeks)	414 days	oil	injection site	sarcoma	4/6[d]

QUALITY OF EVIDENCE

Strengths of Study: The rats were exposed and observed for a significant portion of their lifespan

Weakness of study: No control group, too few experimental animals; irrelevant routes of exposure; no separation by sex; only one species

Overall adequacy: Limited

[a]Source: Druckrey et al., 1966

[b]Mean tumor induction time was 500 days

[c]Metastases to the lung in 3 cases

[d]Metastases to the lung in 1 case

NR = Not reported

TABLE 5-4

Animal Tumor Incidence by Intravenous Injection[a]

Agent: Dimethyl Sulfate

Species/ Strain	Dose	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/BD (n=8)	20 mg/kg	once, day 15 of gestation	1 year	NR	offspring nervous system	malignant	4/59[b]
					offspring liver	hepatic tumor	2/59[b]

QUALITY OF EVIDENCE

Weakness of Study: No controls; 1 year may be too short for detection of all the tumors; small number of animals; irrelevant route of exposure, only one species

Overall Adequacy: Limited

[a]Source: Druckrey, 1973; Druckrey et al., 1970

[b]There was a discrepancy between the results reported in the IARC (1974) review of Druckrey et al. (1970) -- 7/59 offspring with malignant tumors, 3 of which were in the nervous system -- and the results reported in Druckrey (1973) -- 6/59 offspring with malignant tumors, 4 of which were in the nervous system.

NR = Not reported

As reviewed by ACGIH (1980) and IARC (1974), Druckrey et al. (1966) reported few cases of bronchial carcinoma in a group of 7-11 workers exposed to dimethyl sulfate. Thiess et al. (1969) found that 24 workers who had been exposed to dimethyl sulfate for 3 years had no evidence of lung cancer. However, lung cancer developed in 4/368 men who had been occupationally exposed to dimethyl sulfate; statistical analysis was not possible. An E.I. DuPont de Nemours and Co., Inc. (1975) epidemiology study covering 15 years indicated that occupational exposure to dimethyl sulfate did not result in an increased incidence of respiratory tumors. Additional details of these studies were not provided in the ACGIH (1980) and IARC (1974) reviews. An abstract of a report by Bettendorf (1977) described the development of lung cancer in a chemist occupationally exposed to dichlorodimethylether, monochlorodimethylether and small amounts of dimethyl sulfate for 7 years. Albert and Puliafito (1977) reported that a man exposed to dimethyl sulfate for 6 years developed choroidal melanoma.

5.2. MUTAGENICITY

Hoffmann (1980) extensively reviewed the genetic effects of dimethyl sulfate, which does not require metabolic activation to elicit its mutagenicity. In summary, dimethyl sulfate was positive for reverse mutations in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 (Skopek et al., 1978), although Braun et al. (1977) reported a negative result in strains TA1537 and TA1538 and a positive result only with strain TA1535; positive results were reported in repair assays with Escherichia coli (Alderson, 1964; Fluck et al., 1976), for reverse mutation and transforming DNA mutations with Bacillus subtilis (Bresler et al., 1968; Zamenhof and Arikawa, 1970), repair assays with Proteus mirabilis (Adler et al., 1976) and prophage induction with Micrococcus lysodeikticus (Field and

Naylor, 1962), reverse mutations in Saccharomyces cerevisiae (Prakash and Sherman, 1973), Schizosaccharomyces pombe (Heslot, 1961) and Neurospora crassa (Kolmark, 1956), forward mutation in Aspergillus nidulans (Moura Duarte, 1971) and reverse mutation in Ophiostoma multiannulatum (Zetterberg, 1960); sex-linked recessive lethal mutations were reported in Drosophila sp. treated with dimethyl sulfate (Rapoport, 1947; Kolmark, 1956; Alderson, 1964); forward mutations were reported in Chinese hamster ovary cells exposed to dimethyl sulfate (Couch et al., 1978); chromatid aberrations were reported in mouse ascites tumor cells exposed to dimethyl sulfate (Schoneich et al., 1970); sister chromatid exchange (Wolff et al., 1977) and DNA damage (Cleaver, 1977) occurred in human fibroblasts exposed to dimethyl sulfate; dimethyl sulfate inhibited murine testicular DNA synthesis (Seiler, 1977), but did not induce dominant lethal mutations in mice (Epstein and Shafner, 1968). A subsequent paper by Epstein et al. (1972), however, indicated that the mice treated intraperitoneally with 23 or 35 mg/kg of dimethyl sulfate had been mated a total of only 3 weeks, whereas most dominant lethal assays are conducted for 8 weeks (Epstein et al., 1972).

Because dimethyl sulfate is an alkylating agent, known to methylate the purines of DNA (McMahon et al., 1979; Hoffmann, 1980), it has been used as a tool to elucidate the genetics of enzyme induction (Quillardet et al., 1982), recombination (Rich and Goldschmidt, 1980), and repair mechanisms (Matsushima et al., 1978; Morohoshi and Munakata, 1983; Karran, 1979). Scott et al. (1982) reviewed the usefulness in the evaluation of genetic toxicity of the Aspergillus nidulans system in which dimethyl sulfate is mutagenic. An abstract of a German study reported that the effect of alkylating agents on yeast mutagenicity correlates well with the carcinogenicity of alkylating agents; metabolic activation is not required (Obrikat, 1980).

In an attempt to relate the structure of the mutagenic alkylating agents to their biological effects, such as mortality of adults, production of X-chromosome recessive lethal mutations and the induction of reciprocal translocations, Drosophila sp. were treated with dimethyl sulfate, along with several other alkylating agents (Vogel and Natarajan, 1979a,b). Dimethyl sulfate was reported to cause increased cytotoxicity, chromosomal breakage and mosaicism, but a decreased mutagenic effectiveness in comparison with other alkylating agents studied (Vogel and Natarajan, 1979a). Vogel and Natarajan (1979b) concluded that there is a strong relationship between the chemical reactivity of an alkylating agent and its ability to produce chromosomal breakage. The chromosal breaking ability of dimethyl sulfate in Drosophila sp. was confirmed by Sobels et al. (1980). Abstracts of Russian studies indicate that dimethyl sulfate exposure increased the efficiency of selection for decreased Drosophila sp. thorax length (Savchenko and Eliseeva, 1982), but had no effect on the number of abdominal bristles (Savchenko and Eliseeva, 1981).

The exposure of cultured mammalian cells to dimethyl sulfate resulting in the alkylation of DNA and the stimulation of an excision repair mechanism has been reported for human fibroblasts (Brent, 1979; Gruenert and Cleaver, 1981) and rat hepatocytes (Probst and Hill, 1980). Exposure of cultured rat hepatocytes to dimethyl sulfate resulted in unscheduled DNA synthesis (Probst et al., 1981). Cultured Chinese hamster ovary cells have been treated with dimethyl sulfate in vitro to elucidate the relationship between cytotoxicity and mutagenicity (Couch and Hsie, 1976; Suter et al., 1980; Tan et al., 1983; Newman and Miller, 1983; Newbold et al., 1980; and Hsie et al., 1981) and the mechanism of inducing sister chromatid exchange (Connell and Medcalf, 1982; Abe and Sasaki, 1982).

5.3. TERATOGENICITY

In the transplacental carcinogenicity and teratogenicity experiments reported by Druckrey (1973), 20 mg/kg (20% of the LD_{50}) was administered intravenously to eight pregnant rats on day 15 of gestation (Druckrey, 1973; Tomatis, 1973). Of the 59 surviving offspring, four developed malignant tumors of the nervous system and two developed presumably malignant hepatic tumors. The spontaneous incidence of nervous system tumors in rats was reported to be <1 per 1000 (Druckrey, 1973), but no specific control groups were reported. Although no teratogenic effects were reported, Druckrey (1973) emphasized that substances capable of causing cancer when given later in pregnancy are likely to cause embryotoxic or teratogenic effects (or both) when administered early in pregnancy.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of dimethyl sulfate were not located in the available literature cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the previously described study of Schlogel and Bannasch (1970), hamsters, rats and mice were treated by inhalation with dimethyl sulfate at 0.5 or 2.0 ppm for 6 hours/day, 2 days/week bw for 15 months and observed for an additional 15 months. It was reported that all species treated at 2.0 ppm had decreased body weights and that rats and mice treated at 2.0 ppm had increased mortality. Tumors were also observed, but association of tumor occurrence with species or dose was not reported. Furthermore, control data were incompletely reported.

In the Druckrey et al. (1970) study, rats were exposed to 3 or 10 ppm dimethyl sulfate for 1 hour/day, 5 days/week for 130 days (18 weeks) and observed for up to 643 days. Although only 15 of the original 27 rats in

the high dose group survived for 643 days, systemic toxicity effects from dimethyl sulfate exposure were not reported. Furthermore, controls were not used.

5.6. OTHER RELEVANT INFORMATION

Dimethyl sulfate has been reported to alkylate mRNA (Fraenkel-Conrat and Singer, 1980); to enhance the Epstein-Barr virus transformation of cultivated human lymphocytes (Henderson and Fronko, 1984); and to accelerate the transformation of primary cultures of Syrian hamster embryonic cells (Newbold et al., 1982). Intradermal injection of dimethyl sulfate produced depigmentation in C57 black and CBA brown mice, although the effect was greater in black mice (Aw and Boyland, 1981). Case histories (SRC, 1979) indicate that inhalation or percutaneous poisoning with dimethyl sulfate results several hours later in ocular disturbances (blurred vision, redness and swelling of the eyes, and photophobia) followed by severe respiratory symptoms (bronchospasms, pulmonary edema, swelling of the pharyngeal and trachea mucosa, dyspnea).

An abstract of a Russian study reported that rats that inhaled 45 mg/m^3 (LD_{50}) of dimethyl sulfate for 4 hours developed acute respiratory insufficiency accompanied by emphysema, pulmonary edema, focal atelectasis, hemorrhages and interstitial swelling (Batsura et al., 1980). Another abstract of a Russian study indicated that inhalation of dimethyl sulfate by rats may accelerate the aging of the immune system, as evidenced by an increase in platelet-forming cells in the spleen, but not affect the primary immune response (Molodkina and Obbarius, 1981).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Toxicity tests of 96 hours duration were conducted on dimethyl sulfate in a freshwater fish, the bluegill sunfish (Lepomis macrochirus), and an estuarine species, the tidewater silverside (Menidia beryllina) (Dawson et al., 1977). Bluegills were exposed at 7.5-50.0 mg dimethyl sulfate/ℓ for 96 hours, with 7.5 mg/ℓ determined to be the best-fit LC_{50}. Mortality was 10% at the low dose after 96 hours and at 10, 18 and 32 mg/ℓ was 100% within 24 hours. At 50 mg/ℓ mortality was only 30% after 96 hours exposure. Tidewater silversides were exposed at 10, 15 and 18 mg/ℓ for up to 96 hours. Mortality was 0 and 50% at the lower dose levels after 96 hours and 100% after 48 hours of exposure to 18 mg dimethyl sulfate/ℓ. The best-fit LC_{50} for these estuarine fish was 15 mg/ℓ.

6.2. CHRONIC EFFECTS

Pertinent data regarding the toxic effects of chronic exposure to dimethyl sulfate on aquatic species were not located in the available literature cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding the toxic effects of dimethyl sulfate on aquatic plants were not located in the available literature cited in the Appendix.

6.4. RESIDUE

Pertinent data regarding residues of dimethyl sulfate in the aquatic environment or aquatic organisms were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

The mutagenic effects of dimethyl sulfate have been examined in the sperm and eggs of rainbow trout and whitefish (Tsoi, 1969a,b, 1972), common carp (Tsoi et al., 1974), silver carp and bighead (Kormilin et al., 1978). Chromosomal aberrations and abnormal embryonic cells were reported. The LC_{50} for sperm was reported to be 38 mg/ℓ. Offspring of sperm treated with dimethyl sulfate developed mutant scale patterns at a rate 15-25 times the spontaneous mutation rate (Tsoi, 1971). Treatment of female loach at 190 mg dimethyl sulfate/ℓ for 6 hours resulted in high rRNA content in oocytes, which was regarded as activation of rRNA genes (Khvoles et al., 1980).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Based on industrial experience (Thiess et al., 1969; E.I. DuPont de Nemours and Co., Inc., 1975) and the experiments of Druckrey et al. (1966, 1970), the ACGIH (1980) recommended and the ACGIH (1983) has adopted a TWA-TLV of 0.1 ppm (0.5 mg/m³), with an added skin and A_2 notation. The skin notation emphasizes the sensitivity of the cutaneous route of exposure including the eyes and the mucous membranes, particularly those associated with the respiratory system. The A_2 notation emphasizes that dimethyl sulfate is suspected of having carcinogenic potential for humans (ACGIH, 1983). The Occupational Safety and Health Administration's TWA-TLV standard for dimethyl sulfate, also designated with the skin notation, is 1 ppm (5 mg/m³) for an 8-hour work day (Code of Federal Regulations, 1981).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of dimethyl sulfate were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Exposure by inhalation to dimethyl sulfate for 1 hour/day, 5 days/week for 130 days is associated with the induction of nasal cavity carcinomas and nervous system tumors in rats observed for 643 days (Druckrey et al., 1970). No control data, however, were reported. Schlogel and Bannasch (1970) observed malignant tumors of the lungs, thorax and nasal cavity of hamsters, rats and mice exposed to dimethyl sulfate vapor at 0.5 or 2.0 ppm, 6 hours/day, 2 days/week for 15 months and observed for an additional 2 months; the tumor occurrence was not associated with dose or species, and control data were incompletely reported. Rats receiving subcutaneous injections of dimethyl sulfate at a single dose of 50 mg/kg or 8 or 16 mg/kg/week and observed for ~1 year had injection site sarcomas, but control data were not reported (Druckrey et al., 1966, 1970). Tumors of the nervous system and liver developed in the offspring of female rats injected intravenously with dimethyl sulfate at 20 mg/kg on day 15 of gestation (Druckrey, 1973). The incidences of tumors in these studies were presented in Tables 5-1 to 5-4. The lack of, or incomplete reporting of, control data and limited detail provided in the reports precludes the calculation of a q_1^*. Occupational exposure to dimethyl sulfate has been implicated in the development of respiratory tumors (Pell, n.d., Druckery et al., 1966; Thiess et al., 1969; Bettendorf, 1977; E.I. DuPont de Nemous and Co., Inc., 1975) and one case of melanoma (Albert and Pulliafito, 1977); the evidence was only suggestive and not statistically significant. The EPA's Carcinogen Assessment Group has listed dimethyl sulfate as a carcinogen (U.S. DHHS, 1983), and IARC (1982) has indicated that there is sufficient evidence to conclude that dimethyl

sulfate is carcinogenic for experimental animals, but insufficient evidence to reach the same conclusion for humans. Dimethyl sulfate, an alkylating agent, is a known mutagen (Hoffmann, 1980), and has been used recently to elucidate mutagenic mechanisms (Brent, 1979; Connell and Medcalf, 1982; Gruenert and Cleaver, 1981; Karran, 1979; Morohoshi and Munakata, 1983; Probst et al., 1981; Quillardet et al., 1982; Sobels et al., 1980). The teratogenic effects of dimethyl sulfate have not been investigated but, based on the relationship among embryotoxicity, teratogenicity and transplacental carcinogenicity described by Druckrey (1973), administration of dimethyl sulfate between days 8 and 15 of gestation would be expected to cause malformations, while administration of dimethyl sulfate before day 8 of gestation would be expected to result in embryotoxic effects. Pertinent information regarding other reproductive effects of dimethyl sulfate were not located in the available literature cited in the Appendix. Rats exposed by inhalation to dimethyl sulfate at 3 and 10 ppm, 1 hour/day, 5 days/week for 130 days and observed for up to 643 days appeared to have increased mortality due to tumors; no control data were reported (Druckey et al., 1970). Schlogel and Bannasch (1970) observed decreased body weight in hamsters, rats and mice and increased mortality in rats and mice exposed to dimethyl sulfate vapor at 2.0 ppm, 6 hours/day, 2 days/week for 15 months and observed for an additional 15 months. This exposure was also associated with the occurrence of tumors. It was not clear from the abstract whether animals similarly exposed at 0.5 ppm also had tumors, and the control data were incompletely reported. Because the exposures in these studies were associated with tumorigenesis, because control data was absent or incomplete and because details were limited, a NOAEL cannot be defined and calculation of the ADI is precluded.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY

Information on the toxic effect of chronic exposure to dimethyl sulfate is very limited. Increased mortality of rats exposed to dimethyl sulfate by inhalation at 3 or 10 ppm, 1 hour/day, 5 days/week for 130 days and observed for up to 645 days was reported by Druckrey et al. (1970), but these exposures were also associated with nervous system and nasal cavity tumors. Furthermore, control data were not reported. Schlogel and Bannasch (1970) treated hamsters, rats and mice with dimethyl sulfate by inhalation at 0.5 or 2.0 ppm, 6 hours/day, 2 days/week for 15 months and observed them for an additional 15 months. Although decreased body weight gain and increased mortality were observed at 2.0 ppm, the animals also developed tumors. No other studies suitable for RQ ranking of dimethyl sulfate (Table 9-1) were located in the available literature cited in the Appendix.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F = {}^1/ED_{10}$)

The available evidence for the carcinogenicity of dimethyl sulfate was summarized in Section 5.1. and Tables 5-1 to 5-4. Briefly, data from uncontrolled experiments in rats indicated the inhalation exposure to dimethyl sulfate resulted in squamous carcinomas of the nasal cavity, nervous system tumors and lymphosarcomas of the thorax with metastases to the lung (Druckrey et al., 1970). Injection site sarcomas, with metastase to the lungs were observed in rats treated subcutaneously with dimethyl sulfate in other uncontrolled experiments (Druckrey et al., 1966, 1970). Intravenous injection of dimethyl sulfate to pregnant rats was associated with the development of nervous system tumors in the offspring (Druckrey, 1973; Druckrey et al., 1970). Malignant tumors of the lungs, thorax and nasal

TABLE 9-1

Dimethyl Sulfate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ

passages were observed among hamsters, rats and mice exposed to dimethyl sulfate by inhalation (Schlogel and Bannasch, 1970). Control data were incompletely reported.

Occupational exposure to dimethyl sulfate has been implicated in the development of respiratory tumors (Pell, n.d.; Druckrey et al., 1966; Thiess et al., 1969; Bettendorf, 1977; E.I. DuPont de Nemours and Co., Inc., 1975) and one case of choroidal melanoma (Albert and Puliafito, 1977); however, the evidence was neither conclusive nor statistically significant. The available tumor evidence in animals cannot be used to estimate a potency factor because control data were not reported or were incompletely reported and the route of exposure in some cases was irrelevant.

As reflected in the previously prepared Review of Toxicological Data in Support of Evaluation for Carcinogenic Potential of Dimethyl Sulfate (SRC, 1983), the evidence for carcinogenicity in animals is sufficient, while the evidence for carcinogenicity to humans is inadequate, classifying dimethyl sulfate as a group 2B chemical. IARC (1979) also classified dimethyl sulfate as a 2B chemical. Subsequently, however, IARC (1982) has classified dimethyl sulfate as a 2A chemical. Judgments about the weight of evidence involve considerations of the quality and adequacy of the data and the kinds of responses induced by a suspect carcinogen. A system for stratifying the weight of evidence is recommended and based on these guidelines (U.S. EPA, 1984); dimethyl sulfate can be classified as B2, probable human carcinogen.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

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